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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/581,924	06/19/00	ATWELL J	674537-2001

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EXAMINER	
CANELLA,K	
ART UNIT	**PAPER NUMBER**
1642	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/581,924	Atwell et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-89* is/are pending in the applica

4a) Of the above, claim(s) *1-64 and 84-89* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *65-83* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicants election of Group VI with traverse. The traversal is on the grounds that the restriction was improper as Groups I-VII are related to each other and the reference used by the examiner (Better et al, J. Biological Chemistry, 1995, Vol. 270, pp. 14591-14957) to demonstrate lack of unity does not anticipate the current invention(s). Applicant further argues that breaking the instant claims into seven groups would be an undue burden on applicant. Both points have been considered but not found persuasive. Better et al discloses immunofusion proteins comprising only a fragment of human C_{H2}, thus the reference anticipates claim 1 drawn to a chimeric antibody conjugate comprising an antigen binding region of a non-human antibody (murine H65 antibody) and the constant region comprising a non-naturally occurring Fc fragment (truncated C_{H2}). Furthermore, the filing of any patent is voluntary on part of the applicant and as such cannot be considered an undue burden. For these reasons the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made FINAL.

2. Claims 1-89 are pending. Claims 1-64 and 84-89, drawn to non-elected inventions, are withdrawn from consideration. Claims 65-83 are examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 65-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 65 recites "antibody or to one or more groups provided thereon". It is not clear if the applicant intends to encompass non-protein groups such as naturally occurring sugars

which attach to the protein structure of antibodies produced in mammalian cells. For purpose of examination, the claim will be read as encompassing only non-naturally occurring antibody derivatives, such as biotin.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 72-74 and 80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 72 is drawn to a complex formed between (I) an antibody or biologically active fragment thereof derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region which comprises a histadine rich glycoprotein which binds to the antibody of the first species, or to one or more groups provided thereon, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof. The specification teaches the use of bifunctional molecules for labeling antibodies, said molecule having a binding region which binds to an antibody of a first species. Although it is known in the art that a histidine rich glyoprotein has been isolated from human serum, and that this protein interacts with divalent metal ions heparin, thrombospondin and autorosette-forming thymocytes (Morgan, WT., Biochim Biophys Acta, 1978, Vol. 535, pp. 319-333; Lijnen et al, Biochim Biophys Acta, 1983, Vol. 742, pp. 109-115; and Angles-Carno et al, Biochim Biophys Acta, 1992, Vol. 1156, pp. 34-42), the specification does not teach an antibody which would bind to a histidine rich glycoprotein. One of skill in the art would not know how to

use this bifunctional molecule comprising histidine-rich glycoprotein in a binding region for the labeling of an antibody.

Claim 73 is drawn to a complex formed between (I) an antibody or biologically active fragment thereof derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region which binds to groups provided on the antibody of the first species, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof. Further embodiments encompassed by claim 74 are biotin as the group(s) provided on the antibody of the first species, and the binding region comprising strepavidin or fragment thereof. The specification teaches the use of bifunctional molecules for labeling antibodies. In this case the antibody is already labeled with biotin. One of skill in the art would not know how the use of the claimed bifunctional molecule comprising strepavidin would represent an improvement over the well known art of using a biotintylated secondary antibody to react with the antibody of the first species, followed by a reaction with a streptavidin fluorochrome conjugate. The claimed method could not be applied to an antibody in human serum, as biotin would react indiscriminately with all proteins and antibodies in the serum resulting in the binding of a bifunctional molecule comprising strepavidin to all antibodies and proteins in the sample. In order for the claimed bifunctional molecule to label and antibody, the antibody would have to be isolated and reacted with biotin, therefore it is not clear what advantage will be gained from a bifunctional molecule comprising strepavidin in the binding region and at least one C_H domain in the constant region, if the antibody that was to be labeled had been isolated for reaction with biotin. Given the lack of guidance in the specification, one of skill in the art would not know how to use the claimed invention.

Claim 80 is drawn to a complex formed between (I) an antibody or biologically active fragment thereof derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region which binds to groups provided on the antibody of the first species, and (b) a constant region derived from an antibody of a second species, the constant region comprising a

non-naturally-occurring combination of CH domains. The specification teaches these complexes as substitutes for IgG, IgA, or IgM serum, whereby the CH domains can then be recognized by a labeled antibody directed toward the Fc regions of IgG, IgA or IgM. The specification does not teach a further detection method of the complex if the constant region of the bifunctional molecule comprises a non-naturally occurring combination of CH domains. One of skill in the art would be subject to undue experimentation in order to screen secondary antibodies in the development of a method for detecting these complexes.

Claims 65 and 80 are drawn to complexes comprising bifunctional molecules having constant domains comprising CH domains or "epitope thereof". The specification does not disclose any epitopes of CH domains and it cannot be anticipated which fragments of CH domains will function as an epitope in the context of a bifunctional molecule as claimed. The specification does not list or give examples of amino acid residues beyond the known CH domains. Paul (Fundamental Immunology, 3rd Edition, pg. 251, column 1, lines 11-12) states that that to determine an epitope of a protein, knowledge of the three dimensional structure of the protein is required to determine which polypeptides in a given protein would be accessible on the surface of the protein in order for the putative antigenic determinant to be bound by the antibody. In addition, Paul states that mobility of the putative epitope within the native protein structure is also a determining factor for the binding of the epitope to an antibody. Paul points out (supra, pg. 250, lines 4-8) that "Measurement of the mobility in the native proteins largely dependent on the availability of a high resolution crystal structure, so its applicability is limited to only a small subset of proteins." The determination of an "epitope" is clearly a non-trivial enterprise, and without further guidance from the specification on known sequences of the CH domains which have been determined to be epitopes in a specific organism, it would require undue experimentation for one of skill in the art to make and use the invention as claimed.

Claim 71 is drawn to complexes comprising bifunctional molecules wherein the binding region of the bifunctional molecule comprises Fc gamma receptor or a "fragment thereof". The

specification provides no information as to specific fragments of this mouse receptor that would be required to form a complex with an antibody of the first species. Furthermore, there are no teachings in the specification regarding the binding of full length mouse Fc gamma receptor to Fc regions of antibodies from other species. One of skill in the art would be subject to undue experimentation in order to make the claimed complexes comprising the mouse Fc gamma receptor.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 65, 68, 75 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al (J of the National Cancer Institute, 1990, Vol. 82, pp. 1757-1760). Claims 65 and 68 are drawn to a complex formed between (I) an antibody derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region which binds to the antibody of the first species, or to one or more groups provided thereon, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof. Further embodiments encompassed by claims 75 and 76 are the constant region of the bifunctional molecule derived from an IgM molecule and comprising one or more C_H3u domains. Yamamoto et al disclose a mouse anti-idiotypic antibody, 4C10, to human monoclonal antibody L612. Yamamoto et al disclose that 4C10 is secreted from a hybridoma as IgM isotype.

Therefore, Yamamoto et al disclose a complex comprising an antibody from a first species (human monoclonal antibody L612) and a bifunctional molecule compring a binding region and constant regions derived from IgM comprising C_H3u domains (mouse anti-idiotypic antibody 4C10).

9. Claims 65, 68, 77 and 78 are rejected under 35 U.S.C. 102(e) as being anticipated by Muller et al (USP 6,057,421, filed 12/3/97). Claims 65 and 68 are drawn to a complex formed between (I) an antibody derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region which binds to the antibody of the first species, or to one or more groups provided thereon, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof. Further embodiments encompassed by claims 77 and 78 are the constant region of the bifunctional molecule derived from an IgG molecule and comprising one C_H3u domains. Muller et al disclose (column 12, lines 22-25) the mouse anti-idiotypic IgG antibody, 2A11, which bound to the human anti-gp41 antibody. Therefore, Muller et al disclose a complex comprising an antibody from a first species (human anti-gp41 antibody) and a bifunctional molecule compring a binding region and constant regions derived from IgG comprising C_H3g domains (mouse anti-idiotypic antibody 2A11).

10. Claims 65, 68, 81 and 82 are rejected under 35 U.S.C. 102(b) as being anticipated by Zanetti (USP 5,583,202). Claims 65 and 68 are drawn to a complex formed between (I) an antibody derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region which binds to the antibody of the first species, or to one or more groups provided thereon, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof. Further embodiments encompassed by claims 81 and 82 are the constant region of the bifunctional molecule comprising one C_H domain and the first species is a mouse. Zanetti discloses the complex formed between an

SP3B4

engineered antibody comprising peptide structures of immunogenic portions of P. Falciparum as CDR loops and a single C_H1 domain and an antibody of a first species, mouse SP3-B4 (column 9, lines 36-40). Thus Zanetti discloses a complex comprising an antibody from a first species (mouse SP3-B4) and a bifunctional molecule compring a binding region and constant region consisting of C_H1 (ylNANP).

11. Claims 65-68 and 75-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Koren et al (USP 5,560,911). Claims 65 and 68 are drawn to a complex formed between (I) an antibody derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region which binds to the antibody of the first species, or to one or more groups provided thereon, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof. Further embodiments encompassed by claims 75-78 are the constant region of the bifunctional molecule derived from an IgM molecule and comprising one or more C_H3u domains and the constant region of the bifunctional molecule derived from an IgG molecule and comprising one or more C_H3u domains. Additional embodiments encompassed by claims 66 and 67 are affinity constants of less than 10^{-6} M and less than 10^{-8} M, respectively. Koren et al disclose (column 15, lines 47-50) complexes of mouse antiidiotypic antibodies (HAP-SeB8D3, HAP-5eB3B1, HAP-5dE2A2, HAP-5dE2C3, HAP-5eF1D3) which consist of both IgG and IgM isotypes, and human anti-pig antibodies. Koren et al teach the association constants between anti-idiotypic antibodies and their targets vary between 10^8 and 10^{11} M^{-1} (column 7, lines 52-55).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zanetti (USP 5,583,202) in view of Kronvall and Williams (J of Immunology, 1969, Vol. 103, pp.828-833, Bjorck and Kronvall (J of Immunology, 1984, Vol. 133, pp. 969-974) and Atkinson et al (Bioseparation, 1995, Vol. 5, pp. 359-367). Claims 69 and 70 are drawn to a complex formed between (I) an antibody derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region derived from a protein selected from the group consisting of Streptococcal protein G, Staphylococcal protein A and Peptostreptococcal magnus protein L which binds to the antibody of the first species, or to one or more groups provided thereon, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof. Zanetti teaches a complex formed between an engineered antibody comprising peptide structures of immunogenic portions of P. Falciparum as CDR loops and a single C_H1 domain and an antibody of a first species, mouse SP3-B4 (column 9, lines 36-40). Zanetti does not teach an engineered antibody comprising a protein derived from the group consisting of Streptococcal protein G, Staphylococcal protein A and Peptostreptococcal magnus protein L. Kronvall and Williams teach that Staphylococcal protein A binds to the human IgG1, IgG2 and IgG3 subclasses. Bjorck and Kronvall teach that Streptococcal protein G binds all four

human IgG subclasses. Atkinson et al teach that a peptide derived from Peptostreptococcal magnus protein L, Pp1-1, binds L-kappa chains of Ig. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make complexes of bifunctional molecules and antibodies in which the bifunctional molecule comprised a binding region derived from a protein selected from the group consisting of Streptococcal protein G, Staphylococcal protein A and Peptostreptococcal magnus protein L which binds to the antibody of the first species, or to one or more groups provided thereon, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Kronvall and Williams, Bjorck and Kronvall and Atkinson et al on the use of Streptococcal protein G, Staphylococcal protein A and Peptostreptococcal magnus protein L in the specific binding of subtypes of human Ig and L-chains of Ig.

15. Claim 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zanetti (USP 5,583,202) in view of Mezes et al (USP 6,207,815). Claim 79 is drawn to a complex formed between (I) an antibody derived from a first species, and (ii) a bifunctional molecule comprising (a) a binding region which binds to the antibody of the first species, or to one or more groups provided thereon, and (b) a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain, or an epitope thereof derived from an IgA antibody. Zanetti teaches a complex formed between an engineered antibody comprising peptide structures of immunogenic portions of P. Falciparum as CDR loops and a single C_H1 domain and an antibody of a first species, mouse SP3-B4 (column 9, lines 36-40). Zanetti does not teach an engineered antibody comprising one or more C_H domains derived from an IgA antibody. Mezes et al teach that the Ch region of IgA can influence the idiotype of an antibody (column 4, lines 57-63. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the

claimed invention was made to make the engineered antibody of Zanetti having a constant region comprising the C_H region of an IgA antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Mezes et al on the potential contribution of the C_H region of the IgA antibody to the formation of the idiotypic determinant of the binding region in the claimed bifunctional molecule.

Conclusion

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GEETHA P. SANSAL
PRIMARY EXAMINER

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
May 4, 2001